

Introduction: Occam's Razor Is Dull

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Introduction

There is a 3-fold rationale for convening this Symposium on Benzene Metabolism, Toxicity and Carcinogenesis. Benzene is a very important chemical. Among the organic chemicals known to be human carcinogens, benzene is produced in the greatest volume and with the widest possibilities for human exposure in the workplace and in the general environment. Second, there is much recent regulatory activity aimed at setting standards or guidelines to limit the health hazard of this known human leukemogen. Effective public health activity clearly depends upon the best scientific information. Most important, however, is the third rationale for this conference, that this is a very exciting time in the science of benzene toxicology. This excitement will be evident from the presentations, as well as from the number and caliber of the attendees at this meeting.

Accordingly, the goal of this meeting is to present as many as possible of the exciting approaches to benzene research currently being used around the world. To that end, the Organizing Committee has invited presentations from diverse groups with differing scientific approaches and viewpoints; the common theme being the possibility of obtaining insight into the mechanism by which this ubiquitous cornerstone of our chemical era produces its adverse effects in humans.

This is a research conference. Our intention is not to resolve controversy; it is to present whatever controversies exist about the science underlying benzene toxicity to the attendees, with the aim of increasing the likelihood that further scientific studies will address and diminish these uncertainties. It is not a consensus conference, nor do we intend to provide direct advice to regulatory agencies. However, we firmly believe that furthering the understanding of the basic mechanisms of benzene toxicity will inevitably lead to beneficial public health decisions capable of preventing the toxicity of this potent chemical.

Being an introductory speaker in a conference on a subject as broad as benzene is in essence a license to shoot at any target. I will use this license indiscriminately,

choosing different areas based in part upon my own interests, a sense of the need to challenge certain assumptions, and the recognition that many very important areas can be ignored as they will be covered in depth and with much greater expertise by conference participants. What follows is an idiosyncratic approach to the overall topic.

Occam's Razor Is Dull

My major point, and one that I believe summarizes the insight provided by much of the current research, is that Occam's razor is dull. The medieval philosopher William of Occam is known for his very good advice to all experimentalists that the most likely explanation among a group of hypotheses is the simplest one. This has led many of us to seek the single benzene metabolite responsible through a single biochemical mechanism for the production of a specific bone marrow effect resulting in all of the hematological toxicity. My belief is that the major message from this conference will be that benzene toxicity involves more than one metabolite acting through more than one mechanism producing more than biological effect.

Role of Metabolites Derived from Phenol

The evidence for a role in benzene toxicity of polyhydroxylated benzene metabolites, alone or in combination, continues to increase (1,2). Still left unanswered is why administration of phenol does not itself produce overt hematologic toxicity. Formation of polyhydroxylated metabolites from benzene occurs primarily through the initial formation of phenol, yet administering phenol alone, which presumably would produce the same polyhydroxylated metabolites, does not lead to a dose-responsive bone marrow aplasia.

One possible explanation is that benzene effects are due to a combination of one or more hydroxylated metabolites with a ring-opened product, such as muconaldehyde, which would not be formed from phenol alone. Other possibilities exist, including a difference in metabolism of phenol in the presence of benzene. It is important that the

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question of the lack of hematological toxicity of administered phenol be addressed before fully accepting a role for polyhydroxylated benzene metabolites in hematotoxicity.

Chromosomal Effects

One of the more intriguing aspects of benzene toxicology is the fact that it consistently tests negative in most of the short-term assays for mutagenic agents. However, it is indisputable that benzene exposure leads to DNA damage in view of the readily observed cytogenetic abnormalities in humans and in laboratory animals (3). The gross chromosomal abnormalities seen in individuals with benzene hemtotoxicity at first glance suggest major damage to chromosomes or the chromosome sorting process, well beyond what one might expect from epigenetic or promotion-related phenomena. This has for many years suggested to me the possibility that the mechanism of benzene toxicity might include some cross-linking of DNA contents or DNA to nucleohistone. Obviously, there are a number of potential metabolites of benzene, including ring-opened products (4), which could be very efficient cross-linking agents. Biomedical observation of gross chromosomal abnormalities in benzene-exposed individuals should be kept in mind by those who are putting together a mechanism model for benzene toxicity.

Benzene Cancer Biology

There are a number of persistent questions about the biology of benzene-induced cancer that deserve comment. These include the very important point, raised by the studies of Maltoni and those of the NTP, as to whether benzene is a pancarcinogen in humans (5,6). This could conceivably be assessed in humans by thorough evaluation of published large cohort studies of potentially benzene-exposed work forces (e.g., refinery workers) using an increase in the standard mortality ratio for leukemia as a marker for benzene effect in this population. We must also recognize that we still have not fully clarified the likelihood that benzene causes hematological neoplasms other than acute nonlymphocytic leukemia.

Another issue in cancer biology that is potentially of great pertinence to benzene toxicity concerns whether the initiation/promotion/progression tumor model is valid for benzene-induced leukemia.

The frequent observation in humans of benzene-induced aplastic anemia progressing through a preleukemic stage to frank acute myeloblastic leukemia (7) strongly suggests that a tumor progression model would be pertinent to benzene leukemogenesis. However, tumor promotion is more problematic. I am unaware of a classic animal initiation/promotion model for acute myelogenous leukemia. Furthermore, the usual 5- to 10-year latency period for AML following exposure to benzene or other leukemogenic agents is markedly shorter than solid tumor carcinogenesis in humans. Thus, while it is tempting to discuss the effects of benzene metabolites in terms

of tumor initiation and promotion, we must recognize that this model has not yet been shown to be pertinent to human leukemia.

Sensitivity to Benzene

The extent to which individuals differ in their susceptibility to benzene is an important issue. There is no question that some difference in sensitivity will occur, as with any biological variable. However, despite some interesting observations in families (8), I do not believe that there is particularly clear-cut evidence at present of any unique sensitivity—certainly none as great as the idiosyncratic reaction that occurs with chloramphenicol-induced aplastic anemia. Further evaluation of the extent and determinants of human sensitivity to benzene await exploitation of recent advances in benzene toxicology coupled with new understanding of the molecular biology underlying human susceptibility.

Interactive Effects

The observed hematological effects in any individual may not be due to benzene alone. That exposure to benzene by itself can cause aplastic anemia appears unquestionable. It is also highly likely to be a sole cause of acute myelogenous leukemia. However, there is more than ample evidence that other chemicals can interact with benzene (7). Studies of toluene are particularly of interest for two ways. The first is that the interaction is a protective one, as would be predicted by our understanding of benzene metabolism (9). The second is that as benzene and toluene concentrations are lessened to realistic ambient levels, the extent of interaction decreases until it can no longer be detected, including no evidence of interaction at low levels in humans (10). The implications are that not all interactions are additive or synergistic, and that, as might be expected from the known mechanisms of interaction, these are far less likely to occur as concentrations become lower.

Risk Assessment

One can confidently anticipate that the risk assessment quantitatively relating benzene to human leukemia will continue to be a source of much controversy. The ink is hardly dry on the document decreasing the benzene standard from 10 ppm to 1 ppm, about one decade after originally proposed by Eula Bingham, and demands have developed to further decrease this standard. A current risk assessment used by OSHA suggests that a 40-year exposure to 1 ppm benzene in essence doubles the lifetime risk of dying from acute myelogenous leukemia, a risk in the range of 1 in 1000. Thus, the allowable workplace standard leads to a relatively high risk as compared to the usual regulatory approach.

There are a number of points that I believe should be kept in mind when we consider the controversy concern-

ing the risk assessment of benzene. The first is that there is reasonably good agreement among the various risk assessment approaches. In fact, the risk assessment based upon animal data independent of epidemiological studies performed by EPA agrees to the first decimal point with the risk assessment developed from the epidemiological data independent of the animal studies (11). Then why the controversy? Very simply, when I state my belief that there is good agreement among the various risk assessments, this is based upon a data quality objective for risk assessment that defines an order of magnitude as being relatively good agreement. On the other hand, even a 2-fold difference, e.g., between 1 ppm and 0.5 ppm for the current OSHA standard, can be of major importance to the various groups contesting the benzene standard. Unfortunately, there is insufficient data and understanding of benzene to be able to begin to approach what is the micro level for most chemical risk assessment. Accordingly, there is a legitimate reason to carefully review the basis for the existing benzene risk assessment. A major part of the uncertainty in the risk assessment developed from the epidemiological studies is the extent to which human exposure to benzene is accurately depicted. This will be addressed at the present conference. However, let me again emphasize that legitimate arguments that are occurring on the micro scale of risk assessment should not be taken as a reflection of inadequacy in risk assessment at the macro level in which it is usually employed.

Underlying all of the risk assessments for benzene is the assumption that as a carcinogen it is appropriate to use a no-threshold model. What is in fact the likelihood that there is some threshold of regulatory importance for the causation of leukemia by benzene? In as much as water quality standards for benzene are being placed at 1 ppb, perhaps even less now in California under Proposition 0.000065, a threshold of regulatory importance could be relatively low. It is also conceivable that such a threshold, if it exists, could be of regulatory importance for community standards but of no importance toward the workplace standard, which is much higher. A good toxicologist can of course come up with many reasons why a compound such as benzene might have a threshold for its leukemic effects. Rather than discussing these in detail, let me point out what I hope should be obvious by now. It is unrealistic to expect to establish such a threshold through epidemiological studies in view of the powerlessness of the negative in such studies, or through standard animal dose-response studies looking at cancer as an end point simply because of the enormous number of animals that would be necessary even if an appropriate model of acute leukemia was available.

If such a threshold exists, the only way it will be identified is through basic mechanistically oriented research that demonstrates conclusively the pathways by which benzene exposure leads to acute myelogenous leukemia. For those in industry who would like to believe that such a threshold does exist, let me suggest to them that it is only through the support of basic mechanistically oriented research one would be able to discover such a threshold. If in 8 years of the Reagan Administration we

have not changed the regulatory philosophy of the United States that a known human carcinogen is guilty until proven innocent of having no threshold, all of industry's continued lobbying and political effects on behalf of a threshold for a compound such as benzene are simply useless. The funds would much better be spent in the basic research that might show that a threshold of regulatory importance does exist. Even if such research does not show that a threshold of regulatory importance exists, industry has nothing to lose as much as they are now and will undoubtedly in the future be held to such a conclusion.

Exposure Assessment

We need to improve our ability to assess exposure to benzene, from the source to the external portal of entry in humans and from this portal of entry to the target organ. The focus of risk assessment for benzene has been almost exclusively on the hazard side, particularly on determining a unit risk number for cancer. Far less attention has been placed on the exposure side of the dose-response equation. In order to determine risk to society, we need to know more about exposure. Advances in technology have made personal exposure monitors for benzene inhalation much more readily available. There is a reasonable data base to extrapolate the information concerning the amount of benzene that is inhaled that stays in the body. One can make certain presumptions about ingested benzene in water, but far less is known about food, particularly in terms of bioavailability. Even more research is needed to understand the extent to which benzene alone or in a solvent mixture penetrates through the skin. Cross media assessments must take into account the fact that benzene in water can readily off-gas into air so that groundwater contamination with benzene can lead to inhalation as the major route of exposure.

The development of molecular markers based on adducts of benzene metabolite to macromolecules will be powerful tools for exposure assessment. Such markers may be a very useful means of integrating the extent to which human exposure has occurred once pharmacokinetics have been fully worked out. Elucidation of the pharmacokinetics of benzene and its metabolites may also provide very useful markers of exposure through simple tests using urine. For example, urinary phenol has long been used as a marker of benzene exposure, its major drawback being the presence of other sources of phenol in the environment, which makes the test not very specific at relatively low levels of benzene exposure. However, other metabolites of benzene, although present in urine in lower amounts than phenol, may be more specific, as there may not be other environmental sources.

The ideal marker, of course, would be something like carboxyhemoglobin (COHb). COHb provides an integrator of previous exposure over a known period of time, as well as being an end point on the pathway by which carbon monoxide produces its adverse effect.

Toxic Torts

Benzene will get increasing attention in the public eye as a leukemogenic agent because of the activities of the legal profession. The field of toxic torts is one of the major growth industries in America. Approximately 1 out of every 200 Americans die of leukemia. My guess is that one can find a history of significant benzene exposure, whether causally related or not, in at least one out of every five deaths, which translates into about 2000 cases a year. As the legal profession becomes more and more efficient, and as advances in analytical chemistry find benzene in more and more ambient sources, one can expect that a greater percentage of this number of potentially benzene-related cases will come to litigation every year, particularly as a recent jury award in one case was \$108,000,000 (since vacated on appeal). Of all cancers, leukemia is particularly evocative and dreadful to a jury. This tends to increase the likelihood of awards and therefore the likelihood of litigation.

On the other hand, as in all toxic tort situations, the strict "reasonable medical probability" approach (i.e., more likely than not) in essence allows the polluter to increase risk to society by 99% without being held accountable for any of the resultant cases of leukemia. This is also clearly inappropriate public policy. The assistance of the scientific community is greatly needed if we are to be able to deal reasonably as a society with the situation of toxic torts. Advances in such areas as biomarkers and in exposure assessment will greatly assist in the awarding of claims when they are justified and the prevention of spurious claims which do so much to tie up our legal system and increase costs to all.

Summary and Conclusions

Benzene presents one of the most intriguing challenges in our attempts to prevent disease by developing effective regulatory approaches firmly based upon science. The major lesson to be learned from the intense ex-

perience in the past few years is that it is only through research aimed at providing a basic understanding of benzene toxicology can we meet this challenge.

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